REMARKS

Claims 1, 2, 5-15, 18-22 and 56-62 are present in the application and stand rejected. As set forth above, Claims 1, 56, 58, 60, 61, 62, have been amended to provide that the antibacterial composition comprises, in part, an amount of tris (hydroxymethyl) aminomethane effective to maintain the pH of the composition in the range of 7.0 to 9.0 when in contact with the skin injury or surface lesion. Support for this amendment is found in the specification, *inter alia*, at page 23, lines 8-12. It is believed that Claims 1, 2, 5-15, 18-22 and 56-62 are in condition for allowance in view of the foregoing amendments and following comments. Reconsideration and favorable action is requested.

Rejection of Claims 1, 2, 5-9, 12-15, 18, 21, 22 and 56-62 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1, 2, 5-9, 12-15, 18, 21, 22 and 56-62 under 35 U.S.C. 103(a) as being unpatentable over the combined disclosures of Fischetti et al. (U.S. Patent No. 6,423,299, hereafter the Fischetti '299 patent) in view of Raad et al. (U.S. Patent No. 6,267,979, hereafter the Raad '979 patent).

The Examiner has cited the Fischetti '299 patent as teaching a method of inhibiting the proliferation of bacterial infections in various locations including burns and oral mucosa (citing the abstract, claims and Column 8, lines 12-35), wherein a composition comprising a chelating agent and an active antibacterial formulation is applied to the injury (citing the claims, examples and Column 9, line 62, through Column 10, line 5). The Examiner has characterized the Fischetti '299 patent as disclosing that the chelating agents are included in such a way as to synergistically enhance the other components in the formulation. The Examiner has indicated that the Fischetti '299 patent "though disclosing the synergistic relationship of the chelating agents to the remains in formulation is silent to the specific concentration."

The Examiner has cited the Raad '979 patent as disclosing a disinfecting composition comprising a synergistic combination of chelating agents and antimicrobial agents (citing the abstract and example 5). The Examiner has indicated that the chelators of the Raad '979 patent

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

include various EDTA derivatives along with diethylene triamine pentaacetic acid (DPTA) and triethylene tetramine dihydrochloride (TRIEN) while the antibacterial agents include minocycline, oxytetracycline, tetracycline, gentamicin, and erythromycin (citing example 5) and that EDTA is present in concentrations from 0.1-10,000 ppm (citing Column 4, lines 35-40). More specifically, the Examiner has indicated that in one embodiment of the Raad '979 patent the EDTA is present in a concentration of 30 g/L, which is approximately 102 mM (citing example 4). It is the position of the Examiner that the concentration of chelators is merely an optimizable limitation as long as synergy is maintained, and in each embodiment of the Raad '797 patent synergy is maintained.

Finally, the Examiner has characterized the claims of the present application as differing from the cited references by reciting various concentrations of the active ingredient(s), and that the preparation of various compositions having various amounts of the active is within the level of skill of one having ordinary skill in the art at the time of the invention. Using the foregoing analysis, the Examiner concluded that the artisan of ordinary skill would have been motivated to combine the chelating concentration of the Fischetti '299 patent into the treatment method of the Raad '979 patent in order to maintain the synergistic properties of the components and improve the treatment of the infection.

This rejection is respectfully traversed.

The Fischetti '299 patent primarily discloses an aerosol composition for treating *Streptococcus pneumoniae, Haemophilus influenzae* or Streptococcus Group A infections of the respiratory tract by delivering the aerosol to the mouth, throat or nasal passage, although passing is made of other organisms against which lytic enzymes can be targeted and other delivery routes. The active component of the composition of the Fischetti '299 patent is a lytic enzyme genetically coded by a bacteriophage specific for the specific bacteria of the respiratory tract (or other location) to be treated. The invention of the Fischetti '299 patent is based upon the discovery that phage lytic enzymes specific for bacteria infected with a specific phage can break

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

down the cell wall of the bacterium in question. At the same time, the semipurified enzyme is lacking in proteolytic enzymatic activity and therefore non-destructive to mammalian proteins and tissues when present during the digestion of the bacterial cell wall (Column 3, lines 6-12). The Examiner's reference to the Fischetti '299 patent disclosing "the synergistic relationship of the chelating agents to the remains in formulation" apparently is based on Column 11, lines 16-32, which states:

> In order to accelerate treatment of the infection, the therapeutic agent may further include at least one complementary agent which can also potentiate the bactericidal activity of the lytic enzyme. The complementary agent can be penicillin, synthetic penicillins bacitracin, methicillin, cephalosporin, polymyxin, cefaclor. Cefadroxil, cefamandole nafate, cefazolin, cefixime, cefinetazole, cefonioid, cefoperazone, ceforanide, cefotanme, cefotaxime, cefotetan, cefoxitin, cefpodoxime proxetil, ceftazidime, ceftizoxime, ceftriaxone, cefriaxone moxalactam, cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephradine, cefuroximeaxetil, dihydratecephalothin, moxalactam, loracarbef mafate, chelating agents and any combinations thereof in amounts which are effective to synergistically enhance the therapeutic effect of the lytic enzyme.

However, the role of chelating reagents in the enzyme compositions is explained elsewhere in the Fischetti '299 patent. The lytic enzymes of the Fischetti '299 patent are placed in a stabilizing buffer for maintaining the pH of the enzyme composition between a range of about 4.0 to about 9.0. The stabilizing buffer may be a reducing reagent, such as dithiothreitol, a metal chelating reagent, such as ethylenediaminetetracetic acid disodium salt, or it may contain a phosphate or citrate-phosphate buffer. (See the Fischetti '299 patent, Column 5, lines 1-12, Column 6, lines 43-53, and Column 7, lines 53-64.) Thus, amounts of a chelating agent effective to "synergistically enhance the therapeutic effect of the lytic enzyme" as disclosed by the Fischetti '299 patent appear to be amounts (undisclosed) effective to maintain the pH of the composition in the range of about 4.0 to about 9.0 to stabilize the enzymatic activity of the lytic enzyme. The Fischetti '299 patent contains no disclosure or suggestion of inhibiting proliferation of a bacterial population of a skin injury or surface lesion of a patient by contacting the surface of the skin injury or the surface lesion with an antibacterial composition consisting of from

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

0.04 wt % to 25 wt % of a pharmaceutically acceptable antibacterial agent, from 0.1 mM to 100.0 mM a pharmaceutically acceptable chelating agent selected from EDTA, TRIEN and diethyltriamin-pentaacetic acid (DPTA), and an amount of tris (hydroxymethyl) aminomethane effective to maintain the pH of the composition in the range of 7.0 to 9.0 when in contact with the skin injury or surface lesion, wherein the antibacterial agent is present in the composition at a concentration selected to allow synergistic cooperation between the antibacterial agent and the chelating agent, as required by the claims of the present application.

As previously set forth, the Raad '979 patent discloses a method for controlling biofouling in water treatment, pulp and paper manufacture, and oil field water flooding applications with a combination of an antifungal or antibiotic and a chelator (see Field of the Invention, Column 1, lines 12-17), and is unrelated to the field of therapeutic or prophylactic treatment of human or animal subjects. As stated in the Raad '979 patent at Columns 8 and 9:

> The present invention provides compositions and methods for the prevention and treatment of biofouling in water containing or submerged systems. The invention arises from the inventors' discovery that chelators have a significant growth inhibitory effect against species of fungal and bacterial microorganisms including Aspergillus, Fusarium, Candida, Pseudomonas, vancomycin-resistant enterococci, and multidrug resistant Stenotrophomonas (see data in FIG. 1, FIG. 2, FIG. 3, FIG. 4, FIG. 12, FIG. 13 and FIG. 14). Also, the inventors have demonstrated that, when combined with antifungal agents, chelators show additive to synergistic inhibitory activity against the growth of fungal microorganisms (see data in FIG. 5, FIG. 6, FIG. 7, FIG. 8, FIG. 9, FIG. 10 and FIG. 11). The inventors have further demonstrated that, when combined with antimicrobial compounds, chelators show additive to synergistic inhibitory activity against the growth of bacterial microorganisms (see data in FIG. 15, FIG. 16 and FIG. 17). These discoveries provide the basis for a novel program of prevention and treatment of microbial biofoulings using any of several embodiments of the inventive formulations, which may comprise various combinations of chelators, antifungal agents, antiseptic agents, antibacterial agents, and any necessary buffers, solvents, or surfactants.

In addition, the problem sought to be solved is different from that addressed by the present invention. As stated in the Raad '979 patent at Columns 8 and 9:

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

> All pipelines, including those which carry gas, oil, and water or other chemicals become contaminated with bacterial and fungal microorganisms. The same is true for commercial and industrial aqueous process and water handling systems. These microorganisms form biofilm on the surfaces of these pipelines and systems. This biofilm or slime comprises the glycocalyx of the microbial organisms contained therein. Most eukaryotic cells have a carbohydrate-rich zone about their periphery, and this peripheral zone or cell coat is made up of oligosaccharide side chains of glycolipids and integral membrane glycoproteins. Embedded in the biofilm environment, microorganisms such as bacteria and fungi benefit from a form of "extrinsic" resistance, thus rendering organisms which are ordinarily intrinsically and biologically sensitive to antimicrobials more resistant than they would otherwise be.
>
> Colonies that include several kinds of bacteria and fungi can form deposits on metal surfaces, building slime layers and producing organic acids that cause pitting and accelerate corrosion of pipelines and associated metal structures. The inventors have shown that EDTA and other chelators of the present invention assist in disrupting and/or dissolving the glycocalyx of microbial colonies adherent to venous catheters. See, for example, U.S. Pat. No. 5,362,754 by Raad et al., or U.S. patent application Ser. No. 08/317,309 by Raad et al., both of which are herein incorporated by reference. The disruption and/or dissolution of microbial slime improves the activity of antimicrobial compounds against the bacteria, fungi, and other microbes embedded in the slime.

As a further confirmation of the industrial nature of the disclosed methods, the Raad '979 patent discloses at Column 9, lines 26-34:

> In addition, the present invention may be used in conjunction with or may alternate with known biofouling treatments. Such treatments may include, but are not limited to, non-oxidizing biocides such as isothiazolones, formaldehyde and glutaraldehyde. Other concurrent treatments may include the addition of acidic or alkaline compounds to control the pH level, or addition of oxidizing biocides to the water, such as chlorine, chlorine dioxide, chlorine donors, and ozone . . .

As is readily apparent from the foregoing, there is no teaching or suggestion in the Raad '979 patent that the compositions disclosed therein would be biocompatible or could be useful in the treatment of skin injuries or surface lesions of human or animal patients, particularly without damage to the tissue of the patient. It is also apparent that the field of the Raad '979 patent is totally unrelated to the field of invention of the present application and the Fischetti '299 patent. Accordingly, the Raad '979 patent represents nonanalogous prior art and, contrary to the position

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

taken by the Examiner, there is no basis for any person of ordinary skill in the art of wound treatment to look to the field of microbial biofouling in gas, oil, and water applications to modify the teachings of the Fischetti '299 patent. In summary, it is respectfully submitted that the Examiner has improperly combined the disclosure of the Raad '979 patent with the Fischetti '299 patent, and this rejection should properly be withdrawn.

In addition, there is no basis in the generic disclosure of the Raad '979 patent for arriving at the methods of applicants' claims. The applicants have discovered that at specifically controlled (and claimed) levels of an antibacterial agent, a chelating agent and pH, synergistic cooperation occurs between the antibacterial agent and the chelating agent to inhibit proliferation of the bacterial population of a skin injury or surface lesion of a human or animal patient. With respect to chelating agents, the Raad '979 patent discloses at Column 4, lines 35-49:

> The chelators of the present invention may be delivered to an aqueous system at a dosage ranging from about 0.1 parts per million (ppm) to about 10,000 ppm . . . including all fractional dosages therebetween.

With respect to antibiotic agents, the Raad '979 patent discloses at Column 6, lines 45-59:

> The antibiotics of the present invention may be delivered to an aqueous system at a dosage ranging from about 0.01 parts per million (ppm) to about 1000 ppm . . . including all fractional dosages therebetween.

With respect to pH levels, the Raad '979 patent is silent.

As set forth above, the independent claims of the present application require that the antibacterial compositions contain from 0.04 wt % to 25 wt % of the antibacterial agent, from 0.1 mM to 100.0 mM of the chelating agent and an amount of tris (hydroxymethyl) aminomethane effective to maintain the pH of the composition in the range of 7.0 to 9.0 when in contact with the skin injury or surface lesion. Accordingly, even if there were some motivation for a person skilled in the art to modify the cosmetic formulation of the Fischetti '299 patent with the industrial anti-sliming components of the Raad '979 patent, a person skilled in the art would not arrive at the synergistic amounts of antibacterial agent and chelating agent of applicants'

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

claims, and the pH levels at which such synergism is obtained. The discovery of the conditions disclosed and claimed to obtain the highly beneficial results of the present application is not a matter of routine experimentation, as suggested by the Examiner. Rather, the present invention represents a nonobvious advancement in the art of treatment of human or animal skin injuries and surface lesions.

In view of the foregoing amendments and comments, it is respectfully submitted that Claims 1, 2, 5-9, 12-15, 18, 21, 22 and 56-62 would not have been obvious under 35 U.S.C. 103(a) over the combined disclosures of the Fischetti '299 patent in view of the Raad '979 patent, and that this rejection of claims should properly be withdrawn.

Rejection of Claims 1, 2, 8, 9, 11-15, 18-22 and 56-62 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1, 2, 8, 9, 11-15, 18-22 and 56-62 under 35 U.S.C. § 103(a) as being unpatentable over the combined disclosures of the Fischetti '299 patent and the Raad et al. '979 patent, as discussed above, in view of Cuny et al. (U.S. Patent No. 6,207,679 hereafter the Cuny '679 patent). The Examiner has characterized the rejected claims as being drawn to a method of treating specific injuries and has cited the Cuny '679 patent as teaching the use of antimicrobial agents in the treatment of infections (bacterial/fungal) in wounds such as burns, ulcers, scrapes and bruises (citing the abstract, and col. 34, lines 40-55). The formulation comprises various antimicrobial agents such as penicillins, amino glycosides, and cephalosporins along with carriers and chelators such as EDTA (Column 36, lines 7-16; Column 38, lines 19-20). The Examiner concluded that the skilled artisan would have been motivated by these teachings to administer the formulation of the Fischetti '299 patent and the Raad '979 patent combination to the skin for wound treatment as taught by the Cuny '679 patent. It is the Examiner's position that it would have been obvious to follow the suggestions of the Fischetti '299 patent and the Raad '979 patent combination in order to topically treat bacterial infections with an expected result of a method of treating infected wounds.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

The deficiencies in the disclosures of the Fischetti '299 patent and the Raad '979 patent are discussed in detail above and are fully applicable to this rejection.

As discussed in applicants' prior responses, the Cuny et al. '679 patent is directed to new antibacterial compounds--a specifically disclosed family of 2-(3-indolyl)-4-quinolino-carboxamide compounds and their substituted derivatives. Although the Cuny et al. '679 patent contains a generic disclosure of virtually all pharmaceutically acceptable routes of administration of the compounds and does indicate that wetting agents, emulsifiers and lubricants, coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants (including EDTA) can also be present in compositions of the new family of compounds, there is no disclosure or remote suggestion of topically administering a composition containing synergistic concentrations of a pharmaceutically acceptable antibacterial agent and a pharmaceutically acceptable chelating agent selected from EDTA, TRIEN and diethyltriamin-pentaacetic acid (DPTA), together with tris (hydroxymethyl) aminomethane (TRIZMA Base), and a pharmaceutically acceptable carrier, as required by applicants' amended claims. Accordingly, the Cuny et al. '679 patent does not overcome the deficiencies of the Fischetti '299 patent and the Raad '979 patent, as discussed in detail above.

In view of the foregoing amendments and remarks, it is respectfully submitted that Claims 1, 2, 8, 9, 11-15, 18-22 and 56-62 would not have been obvious under 35 U.S.C. § 103(a) over the combined disclosures of the Fischetti '299 patent and the Raad et al. '979 patent in view of the Cuny '679 patent and that this rejection should properly be withdrawn.

Rejection of Claims 1, 2, 5-15, 18, 22 and 56-62 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1, 2, 5-15, 18, 21, 22 and 56-62 under 35 U.S.C. 103(a) as being unpatentable over the Fischetti '299 patent and the Raad '979 patent in view of Kruse et al. (U.S. Patent No. 5,646,151 hereafter the Kruse '151 patent). The Examiner has characterized the rejected claims as being drawn to a method of treating a bacterial infection with a specific biocide.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

The deficiencies in the disclosures of the Fischetti '299 patent and the Raad '979 patent are discussed in detail above and are fully applicable to this rejection.

The Kruse et al. '151 patent does not disclose or suggest either synergistic combinations of antibacterial agents and chelating agents, or the specific compositions of applicants' claimed invention, and does nothing to overcome the basic deficiencies of the Fischetti '299 patent and the Raad '979 patent. Applicants' Claims 1, 2, 5-15, 18, 21, 22 and 56-62 would not have been obvious to any person of ordinary skill in the art within the meaning of 35 U.S.C. § 103(a) over this combination of references. It is believed that the Examiner's rejection of Claims 1, 2, 5-15, 18, 21, 22 and 56-62 should properly be withdrawn.

Provisional Obviousness-Type Double Patenting

The Examiner has provisionally rejected Claims 1, 2, 5-11, and 56-62 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 12-15, 18-21, 25-29, 43 and 44 of copending Application No. 10/739,841. Since both Application No. 10/739,841 and the current application are subject to rejection(s) on other grounds, this rejection will be addressed when nonstatutory obviousness-type double patenting is the only rejection remaining pursuant to MPEP § 804.

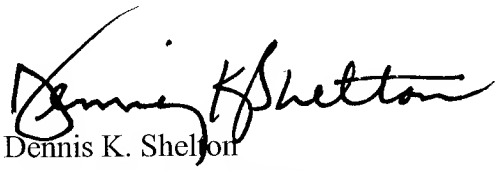
LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

CONCLUSION

In view of the foregoing claim amendments and arguments, applicants respectfully submit that Claims 1, 2, 5-15, 18-22, and 56-62 are in condition for allowance. Reconsideration and favorable action are requested. The Examiner is further requested to contact applicants' representative at the number set forth below to discuss any issues that may facilitate prosecution of this application.

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS[PLLC]



Dennis K. Shelton
Registration No. 26,997
Direct Dial No. 206.695.1718

DKS:cj

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS[PLLC]
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100